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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 12/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/926,391	SHIOJIRI ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-19 and 24-41* is/are rejected.

7)☒ Claim(s) *3 and 20-23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1 and 3-41 are pending.

Applicants' amendment filed October 6, 2005 is acknowledged. Applicant's response has been fully considered. Claims 1 and 24 have been amended. Therefore, claims 1 and 3-41 are examined.

Maintained Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Previous rejection of claims 1, 4-19 and 24-41 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Response to applicant's argument is shown below.

Claims 1, 4-19 and 24-41 are directed to a compound having a naphthyl group and represented by Formula (1), which includes an amino acid compound (when n=0 and m=0 in claim 1, or n=1, m=0 in claim 24), a dipeptide (when n=0, m=1 in claim 1, or n=1, m=0 in claim 24), and a tripeptide (when n=1, m=1 in claim 24); a melanocyte-stimulating hormone (MSH) inhibitory composition, a whitening agent, an immunofunction controlling agent, an appetite controlling agent, or a cosmetic or external preparation for the skin comprising the compound of Formula (1) as the active ingredient. While the specification indicates that the invention

provides di- or tri-peptide derivatives with the Formula (1) having a naphthyl group, which can inhibit the action of melanocyte-stimulating hormone, thereby the compound can be used as an active ingredient in a melanocyte-stimulating hormone inhibitory composition, a whitening agent, an immunofunction controlling agent, an appetite controlling agent, or a cosmetic preparation (pages 3-6), the specification does not disclose a genus of variants for the compounds of Formula (1) including amino acids, dipeptides and tri-peptides having inhibitory activity against MSH and their use as an active ingredient in a MSH inhibitory composition, a whitening agent, an immunofunction controlling agent, an appetite controlling agent, or a cosmetic preparation.

The specification merely discloses specific compounds of Formula (1) such as D-1-Nal-Arg-LeuNH$_2$, D-2-Nal-Arg-LeuNH$_2$, L-1-Nal-Arg-LeuNH$_2$, and L-2-Nal-Arg-LeuNH$_2$ have inhibitory activity against MSH (test Examples 1 and 4), and suppress the melanin formation (text Example 2), it does not identify any active amino acid or dipeptide compound among numerous compounds of Formula (1) (e.g., compounds with undefined substituents in R^1, R^2 and R^3 being a substituted straight-chain or branched-chain C_{1-6} alkyl group having one or more substituents; compounds with undefined substituents in R^4 being a substituted basic amino acid having one or more substituents), nor discloses any particular structure to function/activity relationship in the compounds of formula (1). Furthermore, the specification does not disclose a genus of variants for "functional" compounds of formula (1) including amino acids, dipeptides and tripeptides. The skilled artisan cannot envision all the contemplated compounds of formula (1) having inhibitory activity against MSH based upon four specific naphthyl-tripeptides having Nal-Arg-Leu sequence. Without guidance on the correlation of structure to function/activity for

the compounds of formula (1), one skilled in the art would not know which amino acids, dipeptides or tripeptides in compounds of formula (1) are essential for function/activity, and which compound of formula (1) is functional. The lack of a structure to function/activity relationship in the compounds of formula (1), and the lack of representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

Response to Arguments

Applicants indicate the specification has detailed description at pages 5 and 8-16 of the genus of variants for the compounds of Formula (1), and provides a full and detailed description of how to identify an active amino acid, dipeptide or tripeptide compound within the scope of formula (1) at page 16, line 12 to page 19, line 2; further, pages 19-24 describe how the skilled artisan would prepare compositions containing the compounds meeting the claimed activity limitation; and the specification has exemplified several synthetic methods to produce compounds of Formula (1) and methods by which the activity of the same may be ascertained at pages 25-43; and Test Examples 1, 2, and 4 by which the skilled artisan may readily identify functional compounds (pages 16-17 of the response).

Applicant's response has been considered, however, the argument is not found persuasive because the specification merely describes numerous variants for compounds of formula (1) and identifies four specific Nal-Arg-Leu tripeptides having inhibitory activity against MSH, it has not described a genus of variants for functional compounds of formula (1), nor has established the correlation of structure to function/activity for the compounds of formula (1). For example,

no active naphthyl-containing amino acids or dipeptides have been identified. Although methods to identify an active compound as inhibitor against MSH and synthetic methods to make compounds of formula (1) have been disclosed, the specification has not established the correlation of structure to function/activity for the compounds of formula (1), thus one skilled in the art could not readily identify an active amino acid, dipeptide or tripeptide among numerous compounds of formula (1) without further experimentation. Since applicants have failed to sufficiently describe the claimed invention, a skilled artisan would not recognize applicants were in possession of the claimed invention.

New Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 is indefinite as to R^7 of formula (2) represents an amino acid side chain, which has broader scope than the limitation (i.e., R^7 of formula (2) represents a neutral amino acid having a hydrophobic side chain) cited in the independent claim, claim 24.

Maintained Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Previous rejection of claim 1 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Iwama *et al.* (U.S. Patent 3,619,196) is maintained. Response to applicant's arguments is shown below.

Iwama *et al* teach the preparation of 1-hydroxy-2-naphthoyl-glycine, 1-hydroxy-2-naphthoyl-α-alanine and 1-hydroxy-2-naphthoyl-β-alanine by reacting phenyl-1-hydroxy-2-naphthoate with the corresponding amino acid in the basic condition (column 4, lines 44-69). For example, 1-hydroxy-2-naphthoyl-α-alanine which corresponds to the compound of formula (1), where Ar is 1-naphthyl substituted with hydroxyl group, n is 0, R^2 and R^4 each is H, R^3 is CH_3 (alanine side chain), X^2 is single bond, X^3 is OH, m is 0, and R^9 is H (claim 1); 1-hydroxy-2-naphthoyl-glycine which corresponds to the compound of formula (1), where Ar is 1-naphthyl substituted with hydroxyl group, n is 0, R^2, R^3 and R^4 each is H, X^2 is single bond, X^3 is OH, m is 0, and R^9 is H. Since three different naphthoyl amino acids have been prepared by the same method, it would be obvious that other naphthoyl-amino acid compounds of Formula (I) having R^3 being straight or branched C_{1-6} alkyl group, and R^4 being H can be prepared using the same procedure.

Response to Arguments

Applicants indicate claims 1 and 24 have been amended to define R^4 as being "basic amino acid side chain", and R^7 as being "neutral amino acid having a hydrophobic side chain".

In view of the foregoing amendment, Applicants assert that neither Iwama et al nor Isler discloses or suggest a compound falling within the scope of the presently claimed invention. Applicants also indicate neither Iwama et al nor Isler provides any motivation or suggestion to modify their disclosure to arrive at the claimed invention, thus, the references do not support *prima facie* case of obviousness (pages 15-16 of the response).

Applicants' response has been considered, however, the argument is not found persuasive because the compound of formula (1) having R^4 as being "basic amino acid side chain" does not exclude compounds such as 1-hydroxy-2-naphthoyl-glycine and 1-hydroxy-2-naphthoyl-α-alanine, where R^4 is hydrogen, and R^3 is hydrogen or methyl group (Iwama *et al.*), nor excludes 1-naphthylacetyl-leucine, where R^1, R^6, R^2 and R^4 are each H, and R^3 is isobutyl group (Isler). Regarding the issue of obviousness to make other amino acids, Iwama *et al.* describes the synthesis of 1-hydroxy-2-naphthoyl-glycine, and indicates in the analogous manner, 1-hydroxy-2-naphthoyl-α-alanine can be obtained (column 4, lines 45-67); and Isler describes the synthesis of 1-naphthylacetyl-leucine (Example 2) and 1-naphthylacetyl-glycine (Example 1) and indicates the manufacture of α-naphthyl-acetyl amino acids by reaction of α-naphthyl-acetyl halides with aliphatic amino acids (column 1, lines 7-9). Therefore, the references support *prima facie* case of obviousness that other 1-hydroxy-2-naphthoyl amino acids and 1-naphthylacetyl amino acids having aliphatic side chain (R^4 being H, and R^3 being straight or branched C_{1-6} alkyl group) can be made by the same procedure.

5. Previous rejection of claim 24 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Isler (U.S. Patent 2,179,979) is maintained. Response to applicant's arguments is shown in the paragraph above.

Isler teaches the preparation of 1-naphthylacetyl-leucine by reacting α-naphthyl-acetyl chloride with leucine under alkaline condition (whole page), which corresponds to the compound of formula (1), where Ar is 1-naphthyl, n is 1, X^1 is single bond, R^1, R^6, R^2 and R^4 are each H, R^3 is isobutyl group (leucine side chain), X^2 is single bond, X^3 is OH, m is 0, and R^9 is H (claim 24); Since three different 1-naphthtlacetyl amino acids (e.g., leucine, glycine and sarcosine) have been prepared by the same method, it would be obvious that other naphthylacetyl-amino acid compounds of Formula (I) having R^3 being straight or branched C_{1-6} alkyl group, and R^4 being H can be prepared using the same procedure.

Claim Objections

6. Claims 3 and 20-23 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

7. Claims 1, 4-19 and 24-41 are rejected, and claims 3 and 20-23 are objected to.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner

CHIH-MIN KAM
PATENT EXAMINER

CMK
December 15, 2005